b) dry admixing paroxetine and excipients, compressing the resulting combination into a slug material or roller compacting the resulting combination into a strand material, and milling the prepared material into a free flowing mixture; and

c) compressing the mixture into tablets;

provided that one of the excipients is not microcrystalline cellulose.

19. Tablets according to claim 18 wherein the amount of paroxetine in each tablet is selected from: 10 mg, 20 mg, 30 mg, 40 mg and 50 mg, wherein the amount of paroxetine is expressed as the free base, and wherein a single punch or rotary tablet machine is used to compress the tablets.

REMARKS

Claims 16 to 19 are pending in the application. Claims 18 and 19 have been added in order to more fully claim applicants' invention. Claims 16 and 17 are rejected under 35 U.S.C. §102(b). Claims 16 and 17 are rejected under 35 U.S.C. §103(a). Applicants request reconsideration and withdrawal of the rejections for the reasons set forth herein.

Applicants wish to thank the Examiner and Examiner Gollamudi Kishore for the courtesy extended the undersigned attorney and Mr. Charles Van Horn during the interview which took place on October 3, 2002. In response to the discussions that took place during the interview, applicants submit the instant amendments and remarks.

Applicants note that newly added claims 18 and 19 are directed to a different aspect of the claimed invention, specifically a novel population of tablets that comprise the superior properties of the invention. Applicants respectfully request an independent analysis/allowance of claims 18 and 19 in view of the art of record.

I. Comments Regarding the Information Disclosure Statement

Applicants wish to thank the Examiner for the consideration given the information cited in the IDSs (Documents AA to CEEE) submitted in the instant application. It is

noted on page 2 of the Office Action that the Civil Action documents were considered by the Examiner but not made of record because they are not prior art. Applicants note that failing to qualify as "prior art" is not a valid reason for information not to be made of record. Documents do not have to be prior art to be listed on a Form PTO 1449 and listed on the face of a patent. All of the documents listed in the subject Form PTO 1449s should be made of record in the instant application.

Further, copies of the Forms PTO 1449, with the Civil Action citations crossed out, accompanied the outstanding Office Action. Applicants note that the bottom of the Form PTO 1449 indicates that a line drawn through a citation is an indication that the document was not considered. The Examiner must initial the Form PTO 1449 as an indication that the documents were considered. In order to avoid confusion, applicants respectfully request that copies of the enclosed resubmitted Forms PTO 1449, initialed by the Examiner, accompany the next Office Action.

The interview summary report indicates that the undersigned attorney stated that "arguments being dealt with in the litigation proceedings closely related to the arguments occurring in the prosecution of the current application." This remark must be understood in context. First, this is an accurate statement relative to the issues raised in the prosecution of this application. Second, it is a conclusion reached by the undersigned attorney after consideration of the same documents submitted to the USPTO and independently considered by the Examiner according to the 2d paragraph on page 2 of the Office Action mailed June 4, 2002. Third, the undersigned attorney is involved in the prosecution of pending applications, such as this one, and is covered by the protective order (noted in the 2nd to last paragraph in each IDS) that precludes the sharing of confidential information in the litigation with prosecuting attorneys. Accordingly, the undersigned attorney cannot provide any assurances about information other than the information submitted to the PTO for its independent consideration.

Similarly, the assurances provided by the attorney that "there were no significant arguments present in those proceedings which is not also being dealt with in this application" must be understood in the same context described above. It should not be

taken as a representation that goes beyond the documents submitted to the USPTO in accordance with 37 C.F.R. §§ 1.97 and 1.98.

II. The Rejection of Claims 16 and 17 Under 35 U.S.C. §102(b), in View of Barnes

Claims 16 and 17 are rejected under 35 U.S.C. §102(b) as being anticipated by US 4,721,723 to Barnes et al. (hereinafter Barnes). The Examiner cites several generalized passages in Barnes and urges that the reference anticipates generic claims to a composition comprising paroxetine and excipients. Further, the declaration of Dr. Doughty is indicated as containing personal views instead of scientific data. The Examiner continues to request evidence that indicates the product described in Barnes is made by a wet granulation process. Evidence is requested that indicates the pink hue is detrimental to the pharmaceutical formulation. Additionally, the claims are rejected as product-by-process claims over the generic disclosure in Barnes.

Product-by-process claims are not *per se* anticipated by a generic disclosure. In a proper analysis of a product-by-process claim, the Examiner can not ignore the characteristics or properties that are imparted to the product by the process recited in the claims. Applicants contend that the characteristics and properties imparted to the claimed product by the claimed process (as indicated below) renders the instant invention patentable over the cited reference. If the Examiner persists in rejecting the claimed invention as being anticipated by Barnes, applicants respectfully request that the Examiner offer an analysis as to how the claimed product, including its unique characteristics and properties imparted by the recited process, is anticipated by the generic disclosure in Barnes.

i. The Generalized Passages in Barnes Fail to Provide the Precision Necessary for Anticipating the Instant Claims Under Section 102.

Applicants note the rejection here is one of anticipation under section 102, not obviousness under 103. To anticipate a claim, the reference must teach every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim

is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051 (Fed, Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." Richardson v. Suzuki Motor Co., 9 USPQ2d 1913 (Fed. Cir. 1989). Under a proper analysis, Barnes fails to anticipate the subject claims.

In order for a single reference to render a compound or composition anticipated, the reference must place the compound or composition in possession of the public. That is, the reference must "clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without any need for picking, choosing, and combining various disclosures..." *In re Arkley*, 172 USPQ 524 (CCPA 1972). The reference must therefore provide a certain degree of precision with respect to the specific compound or composition claimed. For example, in *Ex parte Westphal*, 223 USPQ 630 (Bd. Pat. App. 1983), the claim was directed to a composition containing 3-methylthio-4-amino-6-tert-butyl-1,2,4-triazine-5-one. The Examiner rejected the claim under section 102 as anticipated by, inter alia, a patent to Fawzi. This patent disclosed a compound substituted at a particular position with alkyl having 1 to 8 carbon atoms, but did not specifically name the claimed tert-butyl radical. The Board found that the Fawzi patent did not provide the precision necessary for anticipation under section 102. *Id.* at 631.

Similarly, Barnes fails to provide the precision necessary for anticipation under section 102. No pharmaceutical formulations were made in Barnes. Barnes does not even contain a paper example of how to make a pharmaceutical formulation. The Examiner picks and chooses general passages from the reference in concluding anticipation, which is specifically noted in *In re Arkley* as improper in formulating a rejection under section 102.

Moreover, the Examiner is incorrect in considering applicants' claims as "generic claims to a composition comprising paroxetine and excipients" (emphases added) (last sentence of the first full paragraph on page 3 of the outstanding Office Action). Applicants' claims are directed to a specific article (pharmaceutical composition in tablet form, in claims 16 and 17 and tablets, in claims 18 and 19), prepared according to

specified conditions (dry admixing, on a commercial scale etc.). Because the rejection fails to address all of the limitations of the claims, the rejection is improper and should be withdrawn. The phrase "generic claims to a composition" is an extremely broad description that encompasses myriad permutations, and is an inappropriate characterization of applicants' claims. As indicated in the declaration of Dr. David Doughty, pharmaceutical tablets can be prepared by wet and dry methods, and both of these methods can be formulated by granulation or direct compression procedures. As noted in paragraph 8(i) of Dr. Doughty's declaration, each of these methods can impart different physical characteristics to the final tablet.

Additionally, applicants refer to the enclosed pages 1633 to 1658 of Chapter 89 in Remington's Pharmaceutical Sciences, 18th edition, 1990, as a further demonstration of the numerous compositions that are included in the generic usage of the term "tablets". In addition to compressed and coated pharmaceutical tablets, a multitude of other forms are indicated on page 1634 of Remington. Specifically, other forms include Multiple Compressed Tablets, which include Layered Tablets and Press-Coated Tablets. Numerous types of Controlled-Release Tablets including, those which respond to some physiological condition to release the drug, those which release the drug in a relatively steady controlled manner and those that combine combinations of mechanisms to release "pulses" of drug. Further indicated types of Tablets are: Tablets for Solution, Effervescent Tablets, Compressed Suppositories and Inserts, and Buccal and Sublingual Tablets.

Applicants' invention is directed to an article as claimed in claims 16 to 19. In accordance with *Ex parte Westphal*, the generalized passages in Barnes fail to provide the precision necessary for anticipating the instant claims under section 102. In addition, as explained below, the declaration of Dr. Doughty and the affidavits of Dr. Rhodes and Dr. Roman establish that tablets formed on a commercial scale by different processes (dry and wet) are different. Accordingly, the broad reference in Barnes to "conventional methods" cannot serve as a proper basis to anticipate the claimed invention.

ii. The Declaration of Dr. Doughty Fails to Present Scientific Data.

According to the last paragraph on page 3 of the outstanding Office Action, a declaration had been requested to prove that the tablets of the instant claims are patentably distinct from those of the cited art, and that the differences were the result of the dry process described in the claims. Applicants note that the submitted declaration, along with the instant specification, fully comply with the request. First, both papers are signed documents of the inventor, Dr. Doughty. Dr. Doughty states in paragraph 8(i) that pharmaceutical tablets can be formulated by wet or dry methods, that both of these methods can be formulated by granulation of direct compression methods, and that each of these methods can impart different physical characteristics to the final tablet. Dr. Doughty states in paragraph 8(iii) that commercial scale formulations of paroxetine prepared in the absence of water are less likely to develop a pink hue. Based on his experience, Dr. Doughty also states that the reduction in the development of a pink hue in the commercial scale tablet production of paroxetine is related to the formulation being run in the absence of water, and not related to any particular blend of excipients.

iii. Affidavits of Dr. Rhodes and Dr. Roman.

Applicants cite the affidavits of Dr. Christopher T. Rhodes (of record, as being included in reference CAAA, a copy of which is enclosed herewith for the convenience of the Examiner) and Dr. Robin Roman (of record, as being included in reference CBBB, a copy of which is enclosed herewith for the convenience of the Examiner) to further support the patentability of the claimed invention. These affidavits further support the argument that Barnes cannot teach any specific tablets because different products may be formed when different processes are used to form a paroxetine tablet.

Specifically, in paragraph 13 of his affidavit, Dr. Roman indicates that the improvements realized by changing the wet granulation tablet formulation to a dry admixing and compressing process were highly unexpected. At that time, it was thought that because water was always present in the commercial process and the pink hue was only present in some of the batches, if water was the problem, the pink hue would appear

in every batch. Dr. Roman concludes, at paragraph 15, that the instant invention saved time, money, resources and resolved a major regulatory concern in the marketing of paroxetine.

Further, Dr. Rhodes, at paragraph 13 of his affidavit, acknowledges that intermittent stability problems in the context of tablet formulation, such as the pink hue problem experienced with paroxetine, is one of the most difficult to solve. At paragraph 17, he states that reduction of water in the paroxetine manufacturing process would be one of the last factors he, as well as others skilled in the art, would have considered. And he found it a surprising and unexpected discovery that the intermittent pink discoloration was significantly decreased by changing the tableting formulation from wet granulation to dry admixing and compressing. At paragraphs 29, 30 and 32, Dr. Rhodes discusses the different and identifiable physical characteristics that result when tablets are prepared by wet granulation and when they are prepared by dry admixing and compression. Moreover, with regard to paroxetine, Dr. Rhodes concludes in paragraph 32 that the paroxetine tablets prepared by the dry admixing and compression process are superior to tablets made by wet granulation, because the dry admixed and compressed paroxetine tablets are less likely to develop an undesirable pink hue.

In view of the above, applicants contend that it was highly unexpected to discover that the intermittent pink hue problem was ameliorated by removing water from the processing procedure, when water was used in the preparation of all formulations of paroxetine sold at that time. As indicated in paragraphs 29 and 32 of Dr. Rhodes' affidavit, tablets made by the dry process are different and superior to the tablets made by a conventional wet process.

iv. The Request for Evidence That the Product Described in Barnes is Made by a Wet Granulation Process.

Applicants again wish to point out that no pharmaceutical formulations were made in Barnes. The reference broadly refers to conventional teachings but doesn't contain a reference on how to prepare even a single tablet. Barnes does not even contain

a paper example of how to make a pharmaceutical formulation. Because there is no product (pharmaceutical formulation) prepared in Barnes, the Office cannot meet its evidentiary burden to show lack of novelty when there is no indication as to how the product was made. Accordingly, there is no factual basis to support the necessary conclusion that Barnes provides the information necessary to make a paroxetine tablet according to the claimed invention.

Applicants further refer to the affidavit of Dr. Rhodes as an indication of how one skilled in the art would view the disclosure of Barnes. As indicated in the discussion in paragraphs 35 to 39 of Dr. Rhodes' affidavit, if a drug formulator were to make tablets based on the disclosure in Barnes, at the time the Barnes patent application was filed, the tablets would be wet granulated because that was the conventional process at that time.

v. The Request for Evidence that Indicates the Pink Hue is Detrimental to the Pharmaceutical Formulation.

Applicants refer to the affidavits of Dr. Rhodes and Dr. Roman in responding to this request. Dr. Roman was the director in charge of the development of paroxetine hydrochloride formulations form 1991 to 1993 and his affidavit outlines the detrimental effects of the pink hue and the efforts expended to overcome it in the commercial formulation of paroxetine. As indicated in paragraphs 6, 7 and 8 of Dr. Roman's affidavit, the pink hue problem cost SmithKline Beecham millions of dollars in lost revenue and potentially jeopardized the commercial viability of the product. Dr. Rhodes also discussed the problems caused by the pink hue. In paragraphs 13 and 14 of his affidavit, Dr. Rhodes describes the regulatory concerns posed by the pink hue, and indicated that such problems were among the most difficult to solve.

Applicants contend that the evidence presented by the original specification, the declaration of Dr. Doughty, the affidavit of Dr. Roman and the affidavit of Dr. Rhodes sufficiently establish that the pink hue presented significant time, money, resource and regulatory issues regarding the manufacture and sale of paroxetine.

In view of the above, applicants contend that the reference to Barnes fails to anticipate their claimed invention and respectfully request that the rejection be withdrawn.

III. The Rejection of Claims 16 and 17 Under 35 U.S.C. §102(b), in View of Johnson

Claims 16 and 17 are rejected under 35 U.S.C. §102(b) as being anticipated by WO 92/09281 to Johnson (hereinafter Johnson). The Examiner cites several generalized passages in Johnson in urging that the reference anticipates the instant claims. Evidence is requested that shows the presently invented product, as a product-by-process, is patentably distinct from the teaching in Johnson. Evidence is requested that indicates the tablet described in Johnson is made by a process different than the one claimed in the instant application. Evidence is requested regarding whether the tablet made in Johnson contains the pink hue. Evidence is requested that indicates the pink hue is detrimental to the pharmaceutical formulation. Additionally, the claims are rejected as product-by-process claims over the generic disclosure in Johnson.

Product-by-process claims are not *per se* anticipated by a generic disclosure. In a proper analysis of a product-by-process claim, the Examiner can not ignore the characteristics or properties that are imparted to the product by the process recited in the claims. Applicants contend that the characteristics and properties imparted to the claimed product by the claimed process (as indicated below) render the instant invention patentable over the cited reference. If the Examiner persists in rejecting the claimed invention as being anticipated by Johnson, applicants respectfully request that the Examiner offer an analysis as to how the claimed product-by-process, including its unique characteristics and properties, are anticipated by the generic disclosure in Johnson.

i. The Generalized Passages in Johnson Fail to Provide the Precision Necessary for Anticipating the Instant Claims Under Section 102.

Applicants note the rejection here is one of anticipation under section 102, not obviousness under 103. To anticipate a claim, the reference must teach every element of

the claim. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." Richardson v. Suzuki Motor Co., 9 USPQ2d 1913 (Fed. Cir. 1989). Under a proper analysis, Johnson fails to anticipate the subject claims.

In order for a single reference to render a compound or composition anticipated, the reference must place the compound or composition in possession of the public. That is, the reference must "clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without any need for picking, choosing, and combining various disclosures..." *In re Arkley*, 172 USPQ 524 (CCPA 1972). The reference must therefore provide a certain degree of precision with respect to the specific compound or composition claimed. For example, in *Ex parte Westphal*, 223 USPQ 630 (Bd. Pat. App. 1983), the claim was directed to a composition containing 3-methylthio-4-amino-6-tert-butyl-1,2,4-triazine-5-one. The Examiner rejected the claim under section 102 as anticipated by, inter alia, a patent to Fawzi. This patent disclosed a compound substituted at a particular position with alkyl having 1 to 8 carbon atoms, but did not specifically name the claimed tert-butyl radical. The Board found that the Fawzi patent did not provide the precision necessary for anticipation under section 102. *Id.* at 631.

Similarly, Johnson fails to provide the precision necessary for anticipation under section 102. Applicants note that only a single pharmaceutical tablet is alleged to be prepared in Johnson. The Examiner picks and chooses general passages from the reference in concluding anticipation, which is specifically noted in *In re Arkley* as improper in formulating a rejection under section 102.

Moreover, applicants claims are directed to a specific article (pharmaceutical composition in tablet form, in claims 16 and 17 and tablets, in claims 18 and 19), prepared according to specified conditions (dry admixing, on a commercial scale etc.) Because the rejection fails to address all of the limitations of the claims, the rejection is improper and should be withdrawn. The outstanding rejection considers the instant

claims generic to any composition. This is an extremely broad description that encompasses myriad permutations, and is an inappropriate characterization of applicants' claims. As indicated in the declaration of Dr. David Doughty, pharmaceutical tablets can be prepared by wet and dry methods, and both of these methods can be formulated by granulation or direct compression procedures. As noted in paragraph 8(i) of Dr. Doughty's declaration, each of these methods can impart different physical characteristics to the final tablet.

Additionally, applicants refer to the enclosed pages 1633 to 1658 of Chapter 89 in Remington's Pharmaceutical Sciences, 18th edition, 1990, as a further demonstration of the numerous compositions that are included in the generic usage of the term "tablets". In addition to compressed and coated pharmaceutical tablets, a multitude of other forms are indicated on page 1634 of Remington. Specifically, other forms include Multiple Compressed Tablets, which include Layered Tablets and Press-Coated Tablets. Numerous types of Controlled-Release Tablets including, those which respond to some physiological condition to release the drug, those which release the drug in a relatively steady controlled manner and those that combine combinations of mechanisms to release "pulses" of drug. Further indicated types of Tablets are: Tablets for Solution, Effervescent Tablets, Compressed Suppositories and Inserts, and Buccal and Sublingual Tablets.

Applicants' invention is directed to an article in tablet form as claimed in claims 16 to 19. In accordance with *Ex parte Westphal*, the generalized passages in Johnson fail to provide the precision necessary for anticipating the instant claims under section 102.

ii. Evidence is Requested that Indicates the Tablet Described in Johnson is Made by a Process Different than the one Claimed in the Instant Application.

Applicants refer to the affidavit of Dr. Rhodes. As indicated in the Biography of Dr. Rhodes (also of record, as being included in reference CAAA, along with Dr. Rhodes Curriculum Vitae), Dr. Rhodes is a Professor of Applied Pharmaceutical Sciences at the University of Rhode Island. Professor Rhodes has published approximately two hundred

and fifty publications on a variety of pharmaceutical topics associated with the design and evaluation of drug delivery systems and devices. Applicants cite Dr. Rhodes' affidavit as the view of one skilled in the relevant art. As indicated in paragraphs 40 to 44 of Dr. Rhodes affidavit, the only example in Johnson providing a tablet formulation would lead one of skill in the art to make paroxetine tablets by wet granulation. According to Dr. Rhodes (paragraph 42 of the affidavit), the components of the Example 1 tablet formulation are those of the wet granulation commercial product as set forth in SmithKline's New Drug Application. Further, Example 1 of Johnson states that the excipients were mixed together in a conventional manner and compressed in a conventional manner. Dr. Rhodes indicates that, as of 1993, wet granulation was the conventional tableting process (paragraph 43 of the affidavit). He concludes that, when persons of skill in the art see the term "conventional" in Johnson, they would likely think of a wet granulation process. Moreover, the formulation of Example 1 includes "Hydroxypropylmethyl cellulose 2910" (hereinafter HPMC). HPMC is a common cellulose derivative and well known for its use as a wet binder. When HPMC is to be used as a wet binder, it generally makes up from about 5 to 10% weight/weight of the total tablet formulation. The weight of the tablet of Example 1 is 300 mg and includes 15 mg of HPMC, which is 5% of the total tablet weight. Dr. Rhodes concludes (paragraph 44 of his affidavit) that one of skill in the art would infer that the tablet of Example 1 in Johnson is a wet admixed paroxetine tablet.

Thus, in view of the above; specifically

a) that the components of Example 1 are the same as those in the wet granulated commercial product containing paroxetine,

b) that wet granulation was the conventional method of tablet formulation in 1993, and

c) that when HPMC is used as indicated in Example 1 (i.e. at about 5 to 10%) it indicates a wet granulation process is being used,

one of skill in the art would conclude that the tablet of Example 1 in Johnson was prepared using a wet granulation process and that the disclosed tablet is a wet admixed paroxetine tablet.

iii. The Request for Evidence Regarding Whether the Tablet Made in Johnson Contains the Pink Hue.

As indicated in the specification and throughout the prosecution of this application, the pink discoloration problem occurred on an intermittent basis. Not every batch of tablets made displayed the pink hue. In fact, it is the batch to batch variability in the product prepared by the old wet process which caused particular problems from a time, money, resources and regulatory point of view. Also, as indicated in the declaration of Dr. Doughty and the cited portions of Dr. Rhodes affidavit, tablets produced by a wet process will exhibit different characteristics than tablets produced by a dry process. Because the tablets are different, a tablet produced by a wet process does not anticipate a tablet produced by a dry process.

From the record in Johnson that is devoid of any processing details, it is not possible to discern whether or not the single tablet in Johnson contained the pink hue.

iv. The Request for Evidence That Indicates the Pink Hue is Detrimental to the Pharmaceutical Formulation.

In section II, iv of the discussion of Barnes above, applicants addressed the numerous problems that had to be addressed because of the pink hue. Applicants repeat the response here.

In view of the above, applicants contend that the reference to Johnson fails to anticipate their claimed invention and respectfully request that the rejection here be withdrawn.

IV. The Rejection of Claims 16 and 17 Under 35 U.S.C. §102(b), in View of Lassen

Claims 16 and 17 are rejected under 35 U.S.C. §102(b) as being anticipated by EP 269 303 to Lassen (hereinafter Lassen). The Examiner cites several generalized passages in Lassen in urging that the reference anticipates the limitations of the claims, as Lassen is indicated as disclosing a pharmaceutical tablet comprising paroxetine hydrochloride with excipients.

Applicants disagree with the position that Lassen discloses a pharmaceutical tablet comprising paroxetine hydrochloride with excipients. Lassen broadly suggest, at page 2, lines 32 to 38, that the medicament (paroxetine) may be in a variety of forms. But there are no tablets made in Lassen. The cited reference does not even contain a paper example of how to make a pharmaceutical tablet. Lassen contains only general boiler plate language on how to make pharmaceutical formulations. Applicants specifically request that the Examiner cite the passage in Lassen that is referred to as disclosing "a pharmaceutical tablet comprising paroxetine hydrochloride with excipients". As indicated below, the broad general description in Lassen fails to provide the precision necessary for anticipating the instant claims under section 102.

Applicants note the rejection here is one of anticipation under section 102, not obviousness under 103. To anticipate a claim, the reference must teach every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." Richardson v. Suzuki Motor Co., 9 USPQ2d 1913 (Fed. Cir. 1989). Under a proper analysis, Lassen fails to anticipate the subject claims.

In order for a single reference to render a compound or composition anticipated, the reference must place the compound or composition in possession of the public. That is, the reference must "clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without any need for picking, choosing, and combining various disclosures..." *In re Arkley*, 172 USPQ 524 (CCPA 1972). The

reference must therefore provide a certain degree of precision with respect to the specific compound or composition claimed. For example, in *Ex parte Westphal*, 223 USPQ 630 (Bd. Pat. App. 1983), the claim was directed to a composition containing 3-methylthio-4-amino-6-tert-butyl-1,2,4-triazine-5-one. The Examiner rejected the claim under section 102 as anticipated by, inter alia, a patent to Fawzi. This patent disclosed a compound substituted at a particular position with alkyl having 1 to 8 carbon atoms, but did not specifically name the claimed tert-butyl radical. The Board found that the Fawzi patent did not provide the precision necessary for anticipation under section 102. *Id.* at 631.

Similarly, Lassen fails to provide the precision necessary for anticipation under section 102. No pharmaceutical formulations were made in Lassen. Lassen does not even contain a paper example of how to make a pharmaceutical formulation. The Examiner picks and chooses general passages from the reference in concluding anticipation, which is specifically noted in *In re Arkley* as improper in formulating a rejection under section 102.

Moreover, the Examiner is incorrect in considering applicants claims as generic claims to a composition comprising paroxetine and excipients. Applicants claims are directed to a specific article (pharmaceutical composition in tablet form, claims 16 and 17 and tablets, in claims 18 and19), prepared according to specified conditions (dry admixing, on a commercial scale etc.) Because the rejection fails to address all of the limitations of the claims, the rejection is improper and should be withdrawn. Generic claims to a composition is an extremely broad description that encompasses myriad permutations, and is an inappropriate characterization of applicants' claims. As indicated in the declaration of Dr. David Doughty, pharmaceutical tablets can be prepared by wet and dry methods, and both of these methods can be formulated by granulation or direct compression procedures. As noted in paragraph 8(i) of Dr. Doughty's declaration, each of these methods can impart different physical characteristics to the final tablet.

Additionally, applicants refer to the enclosed pages 1633 to 1658 of Chapter 89 in Remington's Pharmaceutical Sciences, 18th edition, 1990, as a further demonstration of the numerous compositions that are included in the generic usage of the term "tablets". In

addition to compressed and coated pharmaceutical tablets, a multitude of other forms are indicated on page 1634 of Remington. Specifically, other forms include Multiple Compressed Tablets, which include Layered Tablets and Press-Coated Tablets. Numerous types of Controlled-Release Tablets including, those which respond to some physiological condition to release the drug, those which release the drug in a relatively steady controlled manner and those that combine combinations of mechanisms to release "pulses" of drug. Further indicated types of Tablets are: Tablets for Solution, Effervescent Tablets, Compressed Suppositories and Inserts, and Buccal and Sublingual Tablets.

Applicants' invention, as claimed, is directed to a specified formulation in tablet form as claimed in claims 16 to 19. In accordance with *Ex parte Westphal*, the generalized passages in Lassen fail to provide the precision necessary for anticipating the instant claims under section 102. In view of the above, applicants respectfully request that the rejection here be withdrawn.

V. The Rejections of Claims 16 and 17 Under 35 U.S.C. §103(a), Over Lassen or Johnson or Barnes

Claims 16 and 17 are rejected under 35 U.S.C. §103(a) as being unpatentable over Lassen or Johnson or Barnes. It is noted that neither Lassen nor Johnson (nor Barnes) gives a specific example teaching applicant's exact method. The rejection is maintained because the cited references are considered to teach applicants claimed product. The Examiner urges that the skilled worker would be motivated to make an oral tablet based on the teachings in the cited references. The Examiner contends that no evidence has been provided to indicate that the cited art used one method of tableting over another. The only difference indicated is applicants' commercial scale limitation, which is considered insufficient to overcome the obviousness rejections.

In order to establish a *prima facie* case of obviousness, the prior art must (1) contain some teaching or motivation that would lead a person skilled in the art to modify the teachings of the reference in a manner that would produce the claimed invention, (2)

show that there is a reasonable expectation of success in such a modification, and (3) teach or suggest all limitations of the claims. See MPEP 2143. Recently, the Federal Circuit has stated that evidence of a teaching, suggestion or motivation to modify must be "clear and particular". See In re Dembiczak, 50 USPQ2d 1614 (Fed. Cir. 1999).

Regarding the teachings in the cited references, applicants note that only Johnson is alleged to disclose the preparation of a single tablet. Lassen and Barnes provide only general descriptions of how to make pharmaceutical formulations.

As indicated in the declaration of Dr. Doughty and the affidavit of Dr. Rhodes, pharmaceutical tablets can be prepared by numerous processes and tablets that are prepared by different processes exhibit different and identifiable characteristics. Specifically, Dr. Doughty, indicates in paragraph 8 (i) of his declaration, that pharmaceutical tablets can be prepared by wet and dry methods and that each of these methods can be formulated by granulation or direct compression procedures. Dr.Rhodes, in paragraphs 29 to 31, describes how the content uniformity and compaction profile of the excipients in tablets will differ depending on the procedure used to make the tablet. In the case of paroxetine, Dr. Rhodes emphasizes that the reduction in the pink hue, realized when the dry process is used, is a characteristic which imparts a superior quality over the tablets made by the old conventional wet granulation process.

As indicated in section III - ii above, the single tablet alleged to be prepared in Johnson is described as being prepared by what the skilled worker would conclude is a wet granulation process. The remaining descriptions in Lassen, Johnson and Barnes provide general boilerplate language on how to prepare pharmaceutical formulations. As such, there is no teaching in any of the cited references that specifically directs the skilled worker to a pharmaceutical tablet formulation. More importantly, the cited references fail to direct the skilled worker to applicants dry process to prepare pharmaceutical tablets containing paroxetine. Accordingly, there is no motivation to modify any of the applied references in a way that would produce the claimed tablets.

The Examiner contends that there is no evidence of record to indicate that the cited art used one method of tableting over another. Applicants agree and have argued

that is one of the reasons that the cited art can not anticipate the claimed invention. As indicated above, the descriptions of the cited art lead the skilled worker to a wet granulated tablet (Johnson) or to a general description of how to make pharmaceutical formulations with no specific formulation (and with no specific tableting process) indicated. Regarding applicants comments indicating that all of the tablets sold have been formulated using a wet granulation process, this teaching is indicated in the specification (and in paragraph 8(ii) of the declaration of Dr. Doughty) by statements of those with personal knowledge. There is nothing in the teachings of Barnes, Johnson or Lassen to lead a person skilled in the art away from a commercial wet granulation process to the dry process used to make the claimed tablets.

As indicated above, all tablet formulations of paroxetine that were sold at the time of the invention were formulated using an aqueous granulation process. On a commercial scale, this process produces unacceptable formulations in that a highly undesirable pink hue is intermittently formed on a batch to batch basis. The current invention is directed to the unexpected discovery that the formulation of paroxetine into tablets can be carried out reliably and on a commercial scale using a formulation process in which water is absent.

It is a well established principle of patent law that unobviousness can reside in the discovery of the cause of a problem, the solution of which employs a combination of old elements. In re Sponnoble 160 USPQ 237 (CCPA 1969). The instant invention resulted from the discovery that the undesirable pink hue produced on a batch to batch basis when paroxetine was formulated via a wet granulation process was alleviated when the composition was formulated in the absence of water. As indicated by the affidavits of Dr. Rhodes and Dr. Roman, this discovery was very surprising and resulted in a superior product. Applicants discovery of the problem is unexpected and their solution, using dry processing, is patentably unobvious over the cited references.

Applicants contend that it was highly unexpected to discover that the intermittent pink hue problem was ameliorated by removing water from the process, when water was always present in the process used to make the formulations of paroxetine sold at that time. Further, as indicated in paragraphs 29 and 32 of Dr. Rhodes' affidavit, the tablets made by the dry process are different and superior to the tablets made by the wet process. Nothing in the cited references anticipates or renders obvious applicants invention.

Applicants therefore submit that all reasons for rejection have been addressed and that the currently pending claims are allowable. Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned attorney at the number indicated below.

Respectfully submitted,

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Enclosures: Form PTO 1449s listing references CB to CEEE
Affidavit of Dr. Rhodes
Affidavit of Dr. Roman
Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Company (1990), Cover, Table of Contents for Chapters 1 to 96, and pages 1633 to 1658 of Chapter 89

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